

Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals

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Abstract Almost 25 centuries ago, Hippocrates, the father of medicine, proclaimed “Let food be thy medicine and medicine be thy food.” Exploring the association between diet and health continues today. For example, we now know that as many as 35% of all cancers can be prevented by dietary changes. Carcinogenesis is a multistep process involving the transformation, survival, proliferation, invasion, angiogenesis, and metastasis of the tumor and may take up to 30 years. The pathways associated with this process have been linked to chronic inflammation, a major mediator of tumor progression. The human body consists of about 13 trillion cells, almost all of which are turned over within 100 days, indicating that 70,000 cells undergo apoptosis every minute. Thus, apoptosis/cell death is a normal physiological process, and it is rare that a lack of apoptosis kills the patient. Almost 90% of all deaths due to cancer are linked to metastasis of the tumor. How our diet can prevent cancer is the focus of this review. Specifically, we will discuss how nutraceuticals, such as allicin, apigenin, berberine, butein, caffeic acid, capsaicin, catechin gallate, celastrol, curcumin, epigallocatechin gallate, fisetin, flavopiridol, gambogic acid, genistein, plumbagin, quercetin, resveratrol, sanguinarine, silibinin, sulforaphane, taxol, γ -tocotrienol, and zerumbone, derived from spices, legumes, fruits, nuts, and vegetables, can modulate inflammatory pathways and thus affect the survival, proliferation, invasion, angiogenesis, and

metastasis of the tumor. Various cell signaling pathways that are modulated by these agents will also be discussed.

Keywords Inflammation · NF- κ B · Nutraceuticals · Therapeutics · Tumorigenesis

1 Introduction

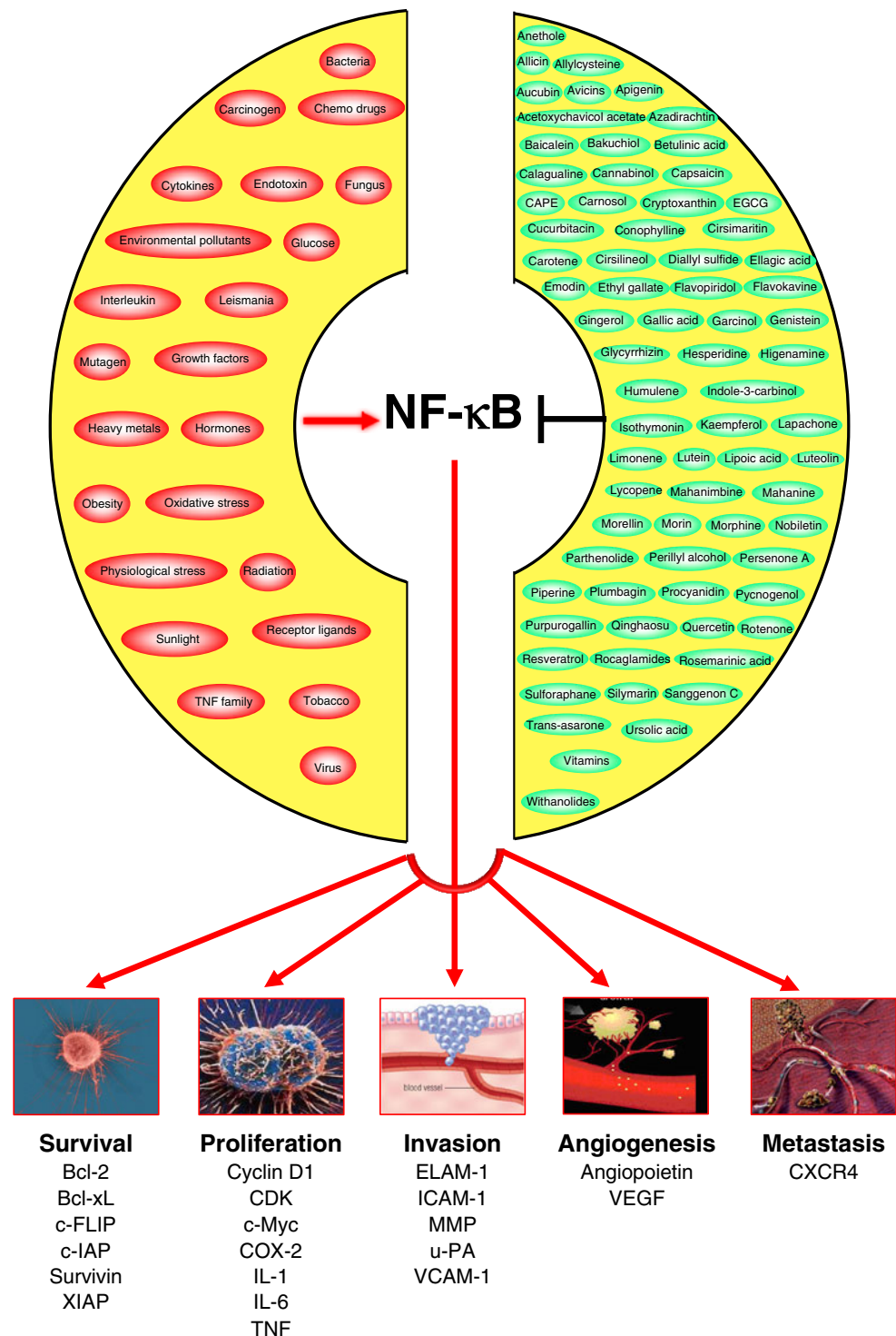
Tumor formation in humans is a multistage process involving a series of events and generally occurs over an extended period. During this process, accumulation of genetic and epigenetic alterations leads to the progressive transformation of a normal cell into a malignant cell. Cancer cells acquire several abilities that most healthy cells do not possess: they become resistant to growth inhibition, proliferate without dependence on growth factors, replicate without limit, evade apoptosis, and invade, metastasize, and support angiogenesis [1]. Although the mechanisms by which cancer cells acquire these capabilities vary considerably among the various types of tumors, most of the physiological changes associated with these mechanisms involve alteration of signal transduction pathways. During the past quarter century, researchers’ understanding of the proteins involved in the various steps of tumor cell development has grown, providing opportunities for identifying new targets for therapeutic development (Fig. 1).

Despite the development of these new therapies, however, cancer remains the second-leading cause of death in the USA and accounts for nearly one in every four deaths. The American Cancer Society estimates that 569,490 Americans will die of cancer in 2010 (www.cancer.org/docroot/stt/stt_0.asp). It is now believed that 90–95% of all cancers are attributed to lifestyle, with the remaining 5–10% attributed to faulty genes [2]. In 2010, for example, about 171,000 cancer

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Fig. 1 Progression of tumor cell development involves survival, proliferation, invasion, angiogenesis, and metastasis. NF- κ B activation regulates tumor cell development by targeting one or more steps in the pathway. Carcinogens activate NF- κ B, whereas nutraceuticals inhibit NF- κ B



deaths will be caused by tobacco use alone. In addition, one third of all cancer deaths in America are attributed to poor nutrition, physical inactivity, overweight, and obesity [3].

Multiple epidemiological and animal studies have shown that consumption of foods rich in fruits and vegetables decreased the occurrence of cancers [4–8]. Almost 30 years ago, Professors Doll and Peto, after conducting an

epidemiological study for the World Health Organization, suggested that appropriate nutrition could prevent approximately 35% of cancer deaths and that up to 90% of certain cancers could be avoided by dietary enhancement [9, 10]. A recent elegant review by Chan and Giovannucci [11] provided an overview of the epidemiological evidence supporting the roles of diet, lifestyle, and medication in

reducing the risk of colorectal cancer. Similarly, a wealth of information is available, implicating dietary agents in cancers of the skin [12], prostate [13, 14], breast [15], lung [16, 17], and gastrointestinal tract [18]. These studies suggest that much of the suffering and death from cancer could be prevented by consuming a healthy diet, reducing tobacco use, performing regular physical activity, and maintaining an optimal body weight.

It is now clear that cancerous phenotypes result from the dysregulation of more than 500 genes at multiple steps in cell signaling pathways [19, 20]. This indicates that inhibition of a single gene product or cell signaling pathway is unlikely to prevent or treat cancer. However, most current anticancer therapies are based on the modulation of a single target. The ineffective, unsafe, and expensive monotargeted therapies have led to a lack of faith in these approaches. Therefore, the current paradigm for cancer treatment is either to combine several monotargeted drugs or to design drugs that modulate multiple targets. As a result, pharmaceutical companies have been increasingly interested in developing multitargeted therapies. Many plant-derived dietary agents, called nutraceuticals, have multitargeting properties. In addition, these products are less expensive, safer, and more readily available than are synthetic agents [19]. Some nutraceuticals are currently in clinical trials (www.clinicaltrials.gov), but others have already been approved for human use [21–23].

A *nutraceutical* (a term formed by combining the words “nutrition” and “pharmaceutical”) is simply any substance considered to be a food or part of a food that provides medical and health benefits [23, 24]. The term *nutraceutical* was coined by Stephen DeFelice in 1989 [23, 25]. During the past decade, a number of nutraceuticals have been identified from natural sources, some of which are shown in Fig. 2. Nutraceuticals are chemically diverse (Fig. 3) and target various steps in tumor cell development (Fig. 4; Table 1).

Because of the vast number of nutraceuticals identified to date, we cannot discuss all of them. We will therefore focus on some of the more promising nutraceuticals in this review, including allicin, apigenin, berberine, butein, caffeic acid, capsaicin, catechin gallate, celastrol, curcumin, epigallocatechin gallate (EGCG), fisetin, flavopiridol, gambogic acid, genistein, plumbagin, quercetin, resveratrol, sanguinarine, silibinin, sulforaphane, taxol, γ -tocotrienol, and zerumbone, in the context of five specific processes of tumorigenesis: survival, proliferation, invasion, angiogenesis, and metastasis. Since chronic inflammation is one of the major mediators of tumor progression and nuclear factor- κ B (NF- κ B) is one of the major inflammatory transcription factors involved in the regulation of various steps of tumor cell development, we will also discuss how nutraceuticals can modulate NF- κ B and can thus affect survival, proliferation, invasion, angiogenesis, and metastasis of the tumor.

2 Regulation of inflammatory pathways by nutraceuticals

During the past two decades, much evidence has emerged, indicating that, at the molecular level, most chronic diseases, including cancer, are caused by a dysregulated inflammatory response [26]. One of the most important links between inflammation and cancer is proinflammatory transcription factor NF- κ B. NF- κ B is a ubiquitous and evolutionarily conserved transcription factor that regulates the expression of genes involved in the transformation, survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells (Fig. 1).

The first clue linking NF- κ B to cancer was the realization that *c-rel*, which is the cellular homolog of the *v-rel* oncogene, encodes a NF- κ B subunit and that all of these proteins share the same DNA binding domain, the Rel homology domain [27]. Constitutively active NF- κ B has now been identified in tissues of most cancer patients, including those with leukemia and lymphoma and cancers of the prostate, breast, oral cavity, liver, pancreas, colon, and ovary [26].

In its resting stage, NF- κ B resides in the cytoplasm as a heterotrimer consisting of p50, p65, and the inhibitory subunit I κ B α [28]. On activation, the I κ B α protein undergoes phosphorylation, ubiquitination, and degradation. p50 and p65 are then released, are translocated to the nucleus, bind specific DNA sequences present in the promoters of various genes, and initiate their transcription. A number of proteins are involved in the NF- κ B signaling pathway. Because of the relevance of the NF- κ B signaling pathway in cancer, this pathway has been proven to be an attractive target for therapeutic development. More than 700 inhibitors of the NF- κ B activation pathway have been reported, including antioxidants, peptides, small RNA/DNA, microbial and viral proteins, small molecules, and engineered dominant-negative or constitutively active polypeptides [29].

During the past two decades, our laboratory and other researchers' laboratories have shown that nutraceuticals can exert anticancer activity by suppressing the NF- κ B signaling pathway. Curcumin, derived from the ancient Indian medicine turmeric, is a widely studied nutraceutical. When human colonic epithelial cells were pretreated with curcumin, inhibition in tumor necrosis factor (TNF)- α -induced cyclooxygenase 2 (COX-2) gene transcription and NF- κ B activation was observed [30]. Curcumin inhibited I κ B degradation through downregulation of NF- κ B-inducing kinase and I κ B kinase (IKK). Curcumin has also been reported to suppress the TNF- α -induced nuclear translocation and DNA binding of NF- κ B in a human myeloid leukemia cell line through suppression of I κ B α phosphorylation and subsequent degradation [31]. Curcumin has been shown to inhibit I κ B α



Fig. 2 Common sources of nutraceuticals, which include spices, legumes, fruits, nuts, and vegetables

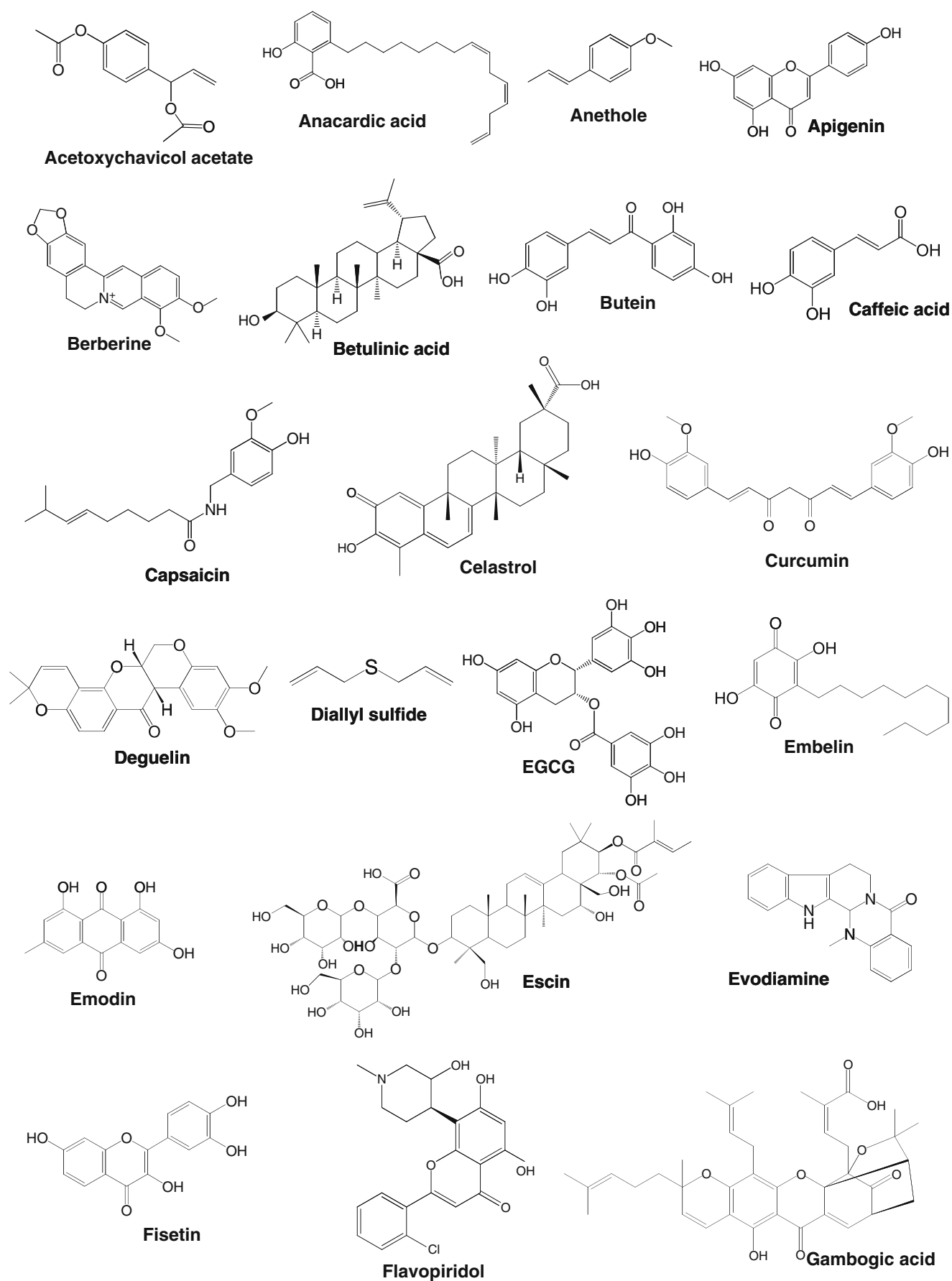


Fig. 3 Chemical structure of nutraceuticals

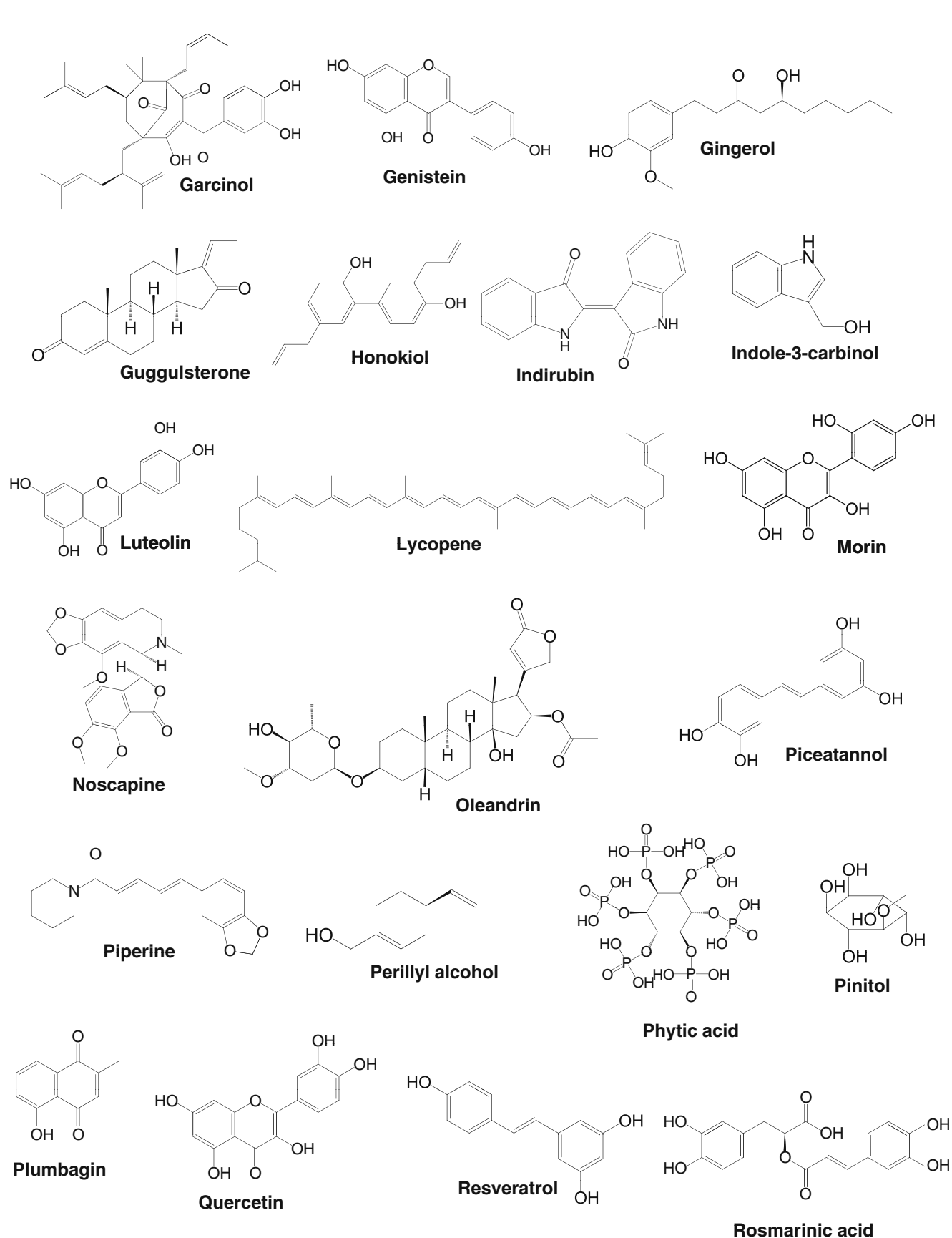


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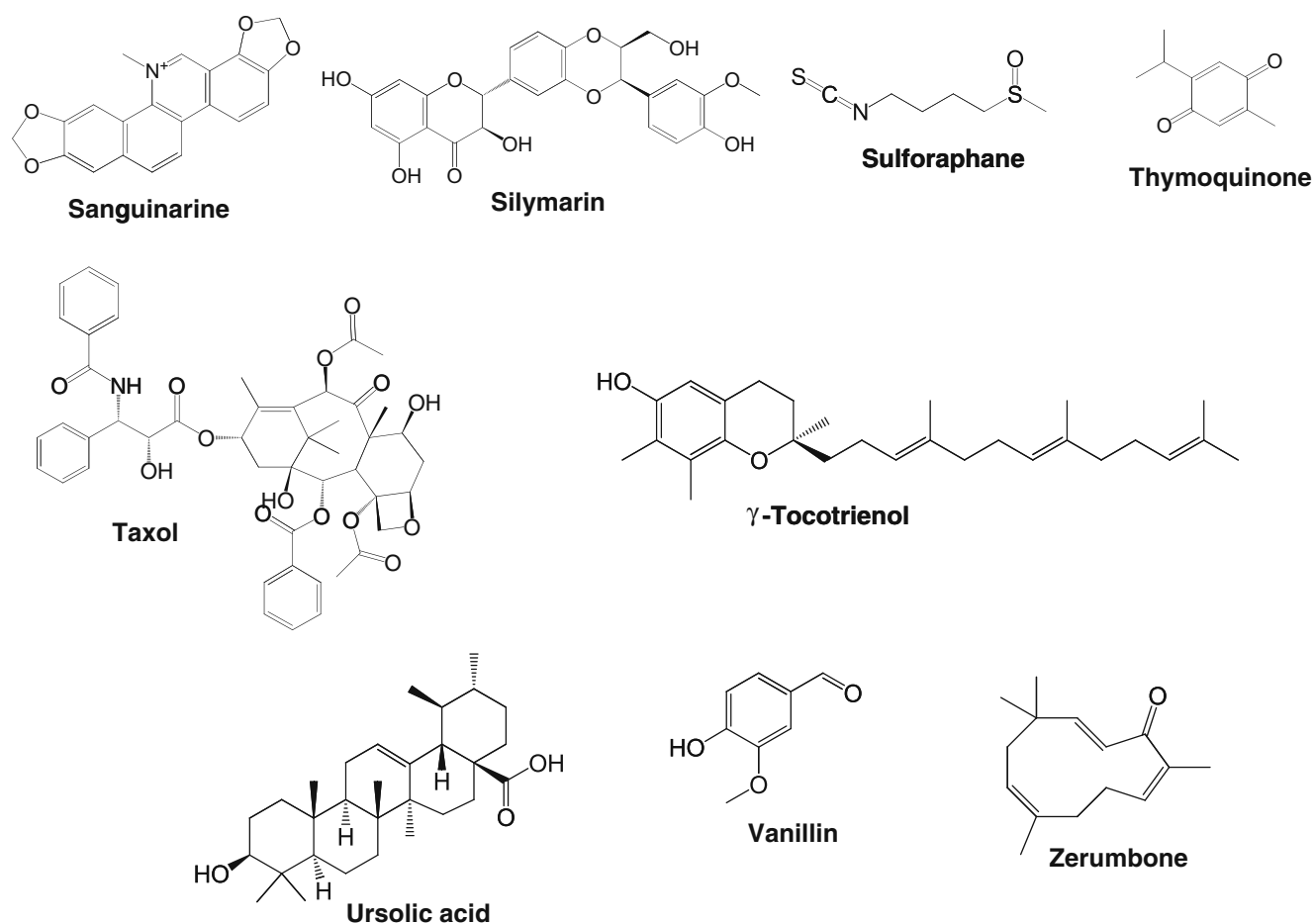


Fig. 3 continued

phosphorylation in human multiple myeloma cells [32] and murine melanoma cells [33] through suppression of IKK activity, which contributed to its antiproliferative, proapoptotic, and antimetastatic activities. Recently, we showed that curcumin has the potential to sensitize human colorectal cancer to capecitabine by modulation of cyclin-D1, COX-2, matrix metalloproteinase (MMP)-9, vascular endothelial growth factor (VEGF), and CXCR4 chemokine receptor 4 (CXCR4) expression in an orthotopic mouse model. This was accompanied by inhibition in NF- κ B activation [34].

Guggulsterone, obtained from the *Commiphora mukul* tree, suppresses NF- κ B activation through inhibition of IKK-dependent I κ B α degradation [35]. Resveratrol, a phytoalexin present in grapes, was shown to induce apoptosis and suppress constitutive NF- κ B in rat and human pancreatic carcinoma cell lines [36]. Mammary tumors isolated from rats treated with resveratrol displayed reduced expression of COX-2 and MMP-9, accompanied by reduced NF- κ B activation [37]. Treatment of human breast cancer MCF-7 cells with resveratrol also suppressed NF- κ B activation and cell proliferation [37]. Capsaicin, a major ingredient of the pepper, has shown chemopreventive

and chemoprotective effects [38–42]. Topical application of capsaicin has been associated with inhibition in phorbol 12-myristate 13-acetate (PMA)-induced mouse skin tumor formation and NF- κ B activation [43]. The inhibitory effect of capsaicin on NF- κ B activation was attributed to

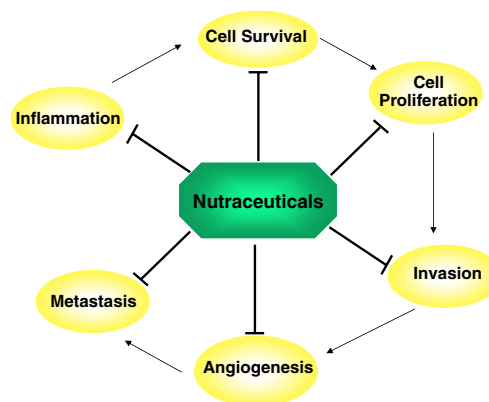


Fig. 4 Targets of nutraceuticals during tumor progression. Nutraceuticals can target survival, proliferation, invasion, angiogenesis, and metastasis steps and can influence various steps of tumor cell development by targeting one or more molecules of inflammation

Table 1 Sources of nutraceuticals and their molecular target linked to cancer

Nutraceuticals (source)	Molecular target
ACA (blue ginger, <i>Alpinia galangal</i>)	Survivin, IAP-1/-2, XIAP, Bcl-2, Bcl-xL, Bfl-1/A1, FLIP, cyclin-D1, c-Myc [95]
Allicin (garlic, <i>Allium sativum</i>)	ICAM-1, FGF2, VEGF [182]
Anacardic acid (cashew, <i>Semecarpus anacardium</i>)	Bcl-2, Bcl-xL, cFLIP, cIAP-1, survivin, cyclin-D1, COX-2 [52]
Apigenin (parsley, <i>Petroselinum crispum</i>)	ICAM-1, HIF-1, VEGF [231, 270]
Berberine (barberry, <i>Berberis vulgaris</i>)	Bcl-2, Bcl-xL, cyclin-D1, c-Myc, FAK, IKK, NF- κ B, u-PA, MMP-2/-9 [59, 60, 271]
Butein (cashew, <i>Semecarpus anacardium</i>)	IAP-2, Bcl-2, Bcl-xL, cyclin-D1, c-Myc, ERK-1/-2, NF- κ B [188, 189]
Caffeic acid (coffee, <i>Coffea arabica</i>)	MMP-9 [190]
Capsaicin (chili pepper, <i>Capsicum</i>)	Bcl-2, Bcl-xL, survivin, E2F, PI3K/AKT/Rac1, VEGF, p38MAPK, p125(FAK), AKT [86, 150, 191, 233]
Catechin gallate (red pine, <i>Pinus resinosa</i>)	MMP-2/-9 [194]
Celastrol (Chinese thunder of god vine, <i>Tripterygium wilfordii</i>)	Bcl-2, Bcl-xL, survivin, cyclin-B1, p21, p27, p38MAPK, FAK [79, 135, 195]
Curcumin (turmeric, <i>Curcuma longa</i>)	IAP-1, Bcl-2, survivin, PAK1, cyclin-D1, VEGF, NF- κ B, AP-1 [125, 234]
EGCG (green tea, <i>Camellia sinensis</i>)	Bcl-2, Bcl-xL, Mcl-1, PI3K/AKT, Ras/ERK, JAK/STAT, NF- κ B, AP-1, u-PA, VEGF, ERK-1/-2 [82, 239, 272]
Evodiamine (Evodia fructus, <i>Evodia</i> spp.)	Bcl-2, Bcl-xL, Mcl-1, cdc25c, cyclin-B1, cdc2, NF- κ B, MMP-9 [96, 136]
Fisetin (smoke tree, <i>Cotinus coggygria</i>)	TAK-1, COX-2, Wnt/EGFR/NF- κ B, ERK-1/-2, MMP-2, u-PA, NF- κ B [144, 204, 273]
Flavopiridol (<i>Dysoxylum binectariferum</i>)	IAP-1, Bcl-2, survivin, CDKs, MMP-2/-9, c-erbB-2, HIF-1 α , VEGF [61, 206, 241, 274]
Gambogic acid (gamboge tree, <i>Garcinia hanburyi</i>)	Bcl-2, p53, p21, ATR, Chk-1, VEGFR2, c-Src, FAK, AKT [63, 137, 242]
Garcinol (kokum, <i>Garcinia indica</i>)	Src, ERK, AKT, nicotinic receptor, cyclin-D3 [64, 275]
Genistein (soybeans, <i>Glycine max</i>)	Bcl-2, Bcl-xL, ATM, Chk-1/-2, cdc25, NF- κ B, AP-1, u-PA, VEGF, FGF-2, NF- κ B, AKT [83, 208, 245]
Indole-3-carbinol (broccoli, <i>Brassica oleracea</i>)	p53, casp-8, E-cadherin, α -, β -, and γ - catenin [65, 210]
Noscapine (Papaveraceae, <i>Papaver rhoeas</i>)	Bcl-2, COX-2 [97, 276]
Plumbagin (Plumbago, <i>Plumbago europaea</i>)	NF- κ B, Bcl-2 [91]
Quercetin (parsley, <i>Petroselinum crispum</i>)	Bcl-xL, cyclin-D1, MMP-2/-9, VEGF, STAT-3 [214, 277]
Resveratrol (red grapes, <i>Vitis vinifera</i>)	Survivin, NF- κ B, MMP-2/-9, VEGF, FGF, MAPK [66, 215, 251]
Sanguinarine (bloodroot, <i>Sanguinaria canadensis</i>)	Bcl-2, MMP-2/-9, VEGF, AKT [67, 69, 253]
Silibinin (milk thistle plant, <i>Silybum marianum</i>)	p53, Bax, Apaf-1, casp-3, CDK-2/-4/-6, cyclin-D1/-D3/-E, p18, p21, p27, MMP-2, u-PA, TIMP-2, NOS, COX, HIF-1 α , VEGF [84, 130, 216, 254]
Sulforaphane (broccoli, <i>Brassica oleracea italica</i>)	Rb-E2F-1, MMPs [133, 219]
Taxol (Pacific yew, <i>Taxus brevifolia</i>)	VEGF [257]
γ -Tocotrienol (Palm, <i>Nigella sativa</i>)	AKT, ERK, MMP-2/-9, TIMP-1/-2, HIF-1 α , VEGF, ERK-1/-2 [220, 258]
Ursolic acid (rosemary, <i>Rosmarinus officinalis</i>)	JNK, AKT, COX-2, cyclin-D1, NF- κ B, MMP-9, VEGF, NO [148, 221, 259]
Vanillin (vanilla bean)	MMP-9, HGF, PI3K/AKT, VEGF [260]
Zerumbone (wild ginger, <i>Zingiber zerumbet</i>)	Bcl-2, cyclin-B1, cdc25c, cdc2, NF- κ B, MMP-9 [81, 139, 223]

ACA acetoxychavicol acetate, AKT AKT8 virus oncogene cellular homolog, AP-1 activator protein 1, Apaf-1 apoptotic protease activating factor 1, ATM ataxia telangiectasia mutated, ATR ataxia telangiectasia and Rad3-related protein, Bax Bcl-2-associated X protein, Bcl-2 B cell lymphoma 2, Bcl-xL B cell lymphoma extra large, casp caspase, cdc25c cell division cycle 25 homolog c (*Schizosaccharomyces pombe*), CDK cyclin-dependent kinase, Chk checkpoint kinase, c-Myc cellular v-myc myelocytomatosis viral oncogene homolog (avian), COX-2 cyclooxygenase 2, E2F elongation 2 factor, EGCG epigallocatechin gallate, EGFR epidermal growth factor receptor, ERK extracellular signal-regulated kinase, FAK focal adhesion kinase, FGF fibroblast growth factor, FLIP FLICE/caspase 8 inhibitory protein, HIF-1 hypoxia-inducible factor 1, HGF hepatocyte growth factor, IAP inhibitor of apoptosis protein, ICAM-1 intercellular adhesion molecule 1, IKK I κ B kinase, JAK Janus-activated kinase, JNK c-Jun N-terminal kinase, MAPK mitogen-activated protein kinase, Mcl-1 myeloid cell leukemia 1, MMP matrix metalloproteinase, NF- κ B nuclear factor kappa B, NO nitric oxide, NOS nitric oxide synthase, PAK1 p21-activated kinase 1, PI3K phosphoinositide 3 kinase, Rac1 Ras-related C3 botulinum toxin substrate 1, Ras Rat sarcoma, Rb retinoblastoma protein, u-PA urokinase-type plasminogen activator, c-Src cellular Rous sarcoma oncogene cellular homolog, STAT signal transducers and activators of transcription protein, TAK-1 TGF- β -activated kinase 1, TIMP tissue inhibitor of metalloproteinases, VEGF vascular endothelial growth factor, VEGFR2 vascular endothelial growth factor receptor 2, Wnt wint, XIAP X-chromosome-linked IAP

blockage of $\text{I}\kappa\text{B}\alpha$ degradation and NF- κB translocation into the nucleus.

Caffeic acid phenethyl ester has been shown to suppress NF- κB activation by suppressing the binding of the p50–p65 complex directly to DNA [44], whereas both sanguinarine and emodin act by blocking the degradation of $\text{I}\kappa\text{B}\alpha$. Alkaloid sanguinarine can prevent phosphorylation and degradation of $\text{I}\kappa\text{B}\alpha$ in response to TNF, phorbol ester, interleukin (IL)-1, or okadaic acid stimulation [45]. Similar to sanguinarine, emodin inhibits TNF-dependent $\text{I}\kappa\text{B}\alpha$ degradation [46]. Recently, emodin was shown to oxidize the redox-sensitive site on NF- κB and prevented NF- κB binding to target DNA in HeLa cells, which was associated with a reduction in tumor size [47].

EGCG, an antioxidant found in green tea, has been shown to suppress malignant transformation in a 12-*O*-tetradecanoylphorbol-13-acetate-stimulated mouse epidermal JB6 cell line, which is mediated by blocking NF- κB activation [48]. EGCG treatment of human epidermal keratinocytes resulted in significant inhibition of ultraviolet-B-induced activation of IKK α , phosphorylation, and subsequent degradation of $\text{I}\kappa\text{B}\alpha$ and nuclear translocation of p65 [49]. More recently, EGCG was found to abrogate p300-induced p65 acetylation *in vitro* and *in vivo*, to increase the level of cytosolic $\text{I}\kappa\text{B}\alpha$, and to suppress TNF- α -induced NF- κB activation. Furthermore, EGCG treatment inhibited the acetylation of p65 and the expression of NF- κB target genes in response to diverse stimuli [50]. Another nutraceutical, gallic acid, obtained from natural products such as gallnuts, sumac, oak bark, and green tea, was recently reported to possess anti-histone acetyltransferase activity, thus showing the potential to downregulate NF- κB activation [51]. Anacardic acid, derived from traditional medicinal plants, can also inhibit NF- κB activation by inhibiting p65 acetylation [52].

Thus, nutraceuticals may block one or more steps in the NF- κB signaling pathway, such as the inhibition of IKK activity, $\text{I}\kappa\text{B}\alpha$ phosphorylation, p65 nuclear translocation, p65 acetylation, and p65 DNA binding. Some nutraceuticals that have the potential to suppress NF- κB activation are shown in Fig. 1. NF- κB can be activated by various carcinogens, some of which are also shown in Fig. 1.

3 Regulation of tumor cell development by nutraceuticals

3.1 Regulation of tumor cell survival by nutraceuticals

Under normal physiological conditions, the human body maintains homeostasis by eliminating unwanted, damaged, aged, and misplaced cells. Homeostasis is carried out in a genetically programmed manner by a process referred to as

apoptosis (programmed cell death) [53–55]. Cancer cells are able to evade apoptosis and grow in a rapid and uncontrolled manner. One of the most important ways by which cancer cells have gained this ability is through mutation in the p53 tumor suppressor gene. Without a functional p53 gene, cells lack the DNA-damage-sensing capability that would normally induce the apoptotic cascade. A complex set of proteins, including caspases, proapoptotic and antiapoptotic B cell lymphoma (Bcl)-2 family proteins, cytochrome c, and apoptotic protease activating factor (Apaf)-1, execute apoptosis either by an intrinsic or extrinsic pathway. The intrinsic pathway is mitochondria dependent, whereas the extrinsic pathway is triggered by death receptors (DRs).

Some antiapoptotic proteins such as Bcl-2 and B cell lymphoma extra large (Bcl-xL) [56] and survivin [57] are overexpressed in a wide variety of cancers. Therefore, selective downregulation of antiapoptotic proteins and upregulation of proapoptotic proteins and p53 in cancer cells offer promising therapeutic interventions for cancer treatment. A number of nutraceuticals have shown potential against tumor cell survival by inducing apoptosis with use of various mechanisms in multiple types of cancer cells (Table 2).

Some of the most common ways that nutraceuticals inhibit survival of tumor cells is by activating caspases, inducing proapoptotic proteins, and downregulating antiapoptotic proteins. Acetoxychavicol acetate, for example, a tropical ginger compound, decreased cell viability in breast-carcinoma-derived MCF-7 and MDA-MB-231 cells through a casp-3-dependent increase in apoptosis [58]. In a recent study, berberine induced apoptosis that was associated with reduction in mitochondrial membrane potential and changes in the Bcl-2-associated X protein (Bax)/Bcl-2 ratio [59]. Berberine also induced casp-3, casp-8, and casp-9 activation and the release of cytochrome c from mitochondria through generation of reactive oxygen species (ROS) [59]. Katiyar et al. [60] showed that berberine can induce apoptosis in A549 and H1299 human lung cancer cells that correlated with disruption of mitochondrial membrane potential, reduction in Bcl-2 and Bcl-xL levels, and increased Bax, Bcl-2 homologous antagonist/killer (Bak), and casp-3 activation.

Flavopiridol, a semisynthetic flavone, was shown to enhance TNF-induced apoptosis through activation of the bid-cytochrome–casp-9–casp-3 pathway in human myeloid cells. This induced apoptosis was associated with inhibited AKT8 virus oncogene cellular homolog (AKT) activation and inhibited expression of various antiapoptotic proteins such as inhibitor of apoptosis protein (IAP)-1, IAP-2, X-chromosome-linked IAP (XIAP), Bcl-2, and Bcl-xL [61]. Gu et al. [62] showed that gambogic acid can induce apoptosis in MCF-7 cancer cells through upregulation of p53 and downregulation of Bcl-2. In human malignant

Table 2 Effect of nutraceuticals on tumor cell survival

Nutraceuticals	Effect
ACA	Suppressed TNF-induced NF- κ B-dependent expression of survivin, IAP-1/2, XIAP, Bcl-2, Bcl-xL, Bfl-1/A1, and FLIP in nonspecific cancer cell type [95]
Anacardic acid	Inhibited Bcl-2, Bcl-xL, cFLIP, cIAP-1, and survivin in various cancer cells [52]
Anethole	Increased the survival time and reduced the weight and volume of tumor in a mice model bearing EAT [278]
Berberine	Reduced Bcl-2 and Bcl-xL levels and increased Bax, Bak, and casp-3 activation in A549 and H1299 human lung cancer cells [60]
β -Escin	Downregulated Bcl-2 and IAP-2 in leukemic and human myeloid cells through inhibition of NF- κ B signaling [103]
Betulinic acid	Decreased the expression of survivin in LNCaP prostate cancer cells through targeted degradation of Sp proteins [75]
Butein	Downregulated the expression of NF- κ B-regulated gene products such as IAP-2, Bcl-2, and Bcl-xL [189]
Capsaicin	Downregulated STAT-3-regulated expression of Bcl-2, Bcl-xL, and survivin in multiple myeloid cells [86]
Celastrol	Enhanced TRAIL-induced apoptosis through the downregulation of cell survival proteins and upregulation of DRs in human breast cancer cells [79]
Coronarlin	Inhibited NF- κ B-regulated expression of IAP-1, Bcl-2, and survivin [100]
Curcumin	Induced apoptosis in prostate cancer cells through downregulation of Bcl-2 and Bcl-XL and upregulation of p53, Bax, Bak, PUMA, Noxa, and Bim [71]
Deguelin	Induced apoptosis in HTLV-1-transformed T cells via inhibition of survivin and STAT-3 phosphorylation through mediation of ubiquitin/proteasome pathway [87]
EGCG	Inhibited survival of EFT through increased expression of Bax and decreased expression of Bcl-2, Bcl-XL, and Mcl-1 proteins and inhibition of IGFIR activity [82]
Embelin	Enhanced TRAIL-mediated apoptosis in malignant glioma cells by downregulation of the short isoform of FLIP [72]
Emodin	Inhibited IL-6-induced JAK2/STAT-3 and induced apoptosis via downregulation of Mcl-1 in myeloid cells [85]
Evodiamine	Reduced survival of cancer cells through downregulation of NF- κ B-dependent antiapoptotic gene products [96]
Fisetin	Induced apoptosis in chemoresistant human pancreatic AsPC-1 cells through suppression of DR3-mediated NF- κ B activation [93]
Flavopiridol	Induced apoptosis in human myeloid cells through activation of the bid-cytochrome-casp-9-casp-3 pathway and inhibition in AKT activation [61]
Gambogic acid	Induced apoptosis, upregulated p53, and downregulated Bcl-2 in MCF-7 cells [62]
Garcinol	Induced apoptosis through downregulation of NF- κ B signaling in breast cancer cells [90]
Genistein	Induced apoptosis in human ovarian cancer cells by phosphorylation and activation of p53 and decrease in the ratios of Bcl-2/Bax and Bcl-xL/Bax [83]
Indirubin	Enhanced TNF-induced apoptosis through modulation of NF- κ B signaling pathway in various cancer cells [98]
Indole-3-carbinol	Induced apoptosis through activation of p53 and caspase pathway in A549 cells [65]
Isodeoxyelephantopin	Potentiated apoptosis through suppression of NF- κ B-regulated gene products in various cancer cells [99]
Noscapine	Sensitized leukemic cells to chemotherapeutic agents and cytokines by modulating the NF- κ B signaling pathway and inducing apoptosis [97]
Oleandrin	Sensitized lung cancer cells to TRAIL-induced apoptosis by upregulating DR4 and DR5 [76]
Plumbagin	Induced apoptosis in human breast cancer cells through inactivation of NF- κ B and downregulation of Bcl-2 [91]
Resveratrol	Downregulated survivin and induced apoptosis in human multidrug-resistant SPC-A-1/CDDP cells [66]
Sanguinarine	Induced apoptosis in human leukemic U937 cells via Bax upregulation, Bcl-2 downregulation, and casp-3 activation [69]
Silymarin	Inhibited survival of hepatic carcinoma cells by upregulating p53, Bax, Apaf-1, and casp-3 and downregulating Bcl-2 and survivin [84]
Sulforaphane	Inhibited growth of orthotopically implanted PC-3 tumors through upregulation of DR4, DR5, Bax, and Bak and inhibition of NF- κ B, PI3K/AKT, and MEK/ERK activation pathways [94]
Thymoquinone	Suppressed NF- κ B-dependent antiapoptotic gene products in various cancer cells [101]
γ -Tocotrienol	Suppressed NF- κ B-dependent antiapoptotic gene products and potentiated apoptosis in various cancer cells [102]
Withanolides	Potentiated apoptosis in cancer cells through suppression of NF- κ B activation and NF- κ B-regulated antiapoptotic proteins [104]

Table 2 (continued)

Nutraceuticals	Effect
Xanthohumol	Induces apoptosis in human colon cancer cells through upregulation of casp-3, casp-8, and casp-9 activation and downregulation of Bcl-2 expression [74]
Zerumbone	Induced apoptosis in HepG2 cells by upregulating Bax protein and downregulating Bcl-2 [81]

ACA acetoxychavicol acetate, *Apaf-1* apoptotic protease activating factor 1, *Bak* Bcl-2 homologous antagonist/killer, *Bax* Bcl-2-associated X protein, *Bcl-2* B cell lymphoma 2, *Bcl-xL* B cell lymphoma extra large, *Bim* Bcl-2-interacting mediator of cell death, *Bfl-1/A1* Bcl-2-related gene expressed in fetal liver protein A1, *casp* caspase, *DR* death receptor, *EGCG* epigallocatechin gallate, *EAT* Ehrlich ascites tumor, *EFT* Ewing family tumors, *ERK* extracellular signal-regulated kinase, *FLIP* FLICE/caspase 8 inhibitory protein, *HTLV-1* human T cell leukemia virus type 1, *IAP* inhibitor of apoptosis protein, *IGFIR* insulin-like growth factor I receptor, *IL-6*, interleukin 6, *JAK* Janus-activated kinase, *Mcl-1* myeloid cell leukemia 1, *MEK* MAPK/ERK kinase, *NF- κ B* nuclear factor kappa B, *Noxa* PhoRbol-12-myristate-13-acetate-induced protein 1, *PI3K* phosphoinositide 3 kinase, *PUMA* p53 upregulated modulator of apoptosis, *Sp* specificity protein, *STAT* signal transducers and activators of transcription protein, *TNF* tumor necrosis factor, *TRAIL* TNF-related apoptosis-inducing ligand, *XIAP* X-chromosome-linked IAP

melanoma A375 cells, gambogic acid induced apoptosis that was associated with increased Bax expression and decreased Bcl-2 expression [63]. Garcinol was shown to induce apoptosis through inhibition of tyrosine phosphorylation of focal adhesion kinase (FAK) and downregulation of Rous sarcoma oncogene cellular homolog (Src), extracellular signal-regulated kinase (ERK), and AKT survival signaling in human colorectal cancer cell line HT-29 [64]. Indole-3-carbinol induced apoptosis through activation of p53 and cleavage of casp-3, casp-8, and casp-9 in lung cancer A549 cells [65].

Resveratrol induced apoptosis in human multidrug-resistant SPC-A-1/CDDP cells associated with downregulation in survivin [66]. Sanguinarine sensitized human gastric adenocarcinoma AGS cells to TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis via downregulation of AKT and activation of casp-3 [67]. In MDA-MB-231 human breast carcinoma cells, sanguinarine induced apoptosis through mediation of ROS production, decrease in mitochondrial membrane potential, release of cytochrome c, activation of casp-3 and casp-9, and downregulation of antiapoptosis proteins XIAP and cIAP-1 [68]. Human leukemia U937 cells, when treated with sanguinarine, induced apoptosis through upregulation of Bax, induction of caspase activation, and downregulation of Bcl-2 [69]. Curcumin, the major polyphenol present in turmeric, is a potent inducer of apoptosis in cancer cells. Curcumin induces upregulation of proapoptotic proteins such as Bax, Bcl-2-interacting mediator of cell death (Bim), Bak, p53 upregulated modulator of apoptosis (Puma), and PhoRbol-12-myristate-13-acetate-induced protein 1 (Noxa) and downregulation of the antiapoptotic proteins Bcl-2 and Bcl-xL [70, 71].

Embelin was shown to enhance TRAIL-mediated apoptosis in malignant glioma cells by downregulation of the short isoform of FLICE/caspase-8 inhibitory protein [72]. Xanthohumol (XN), a chalcone, enhanced TRAIL-induced

apoptosis in prostate cancer cells [73]. In human colon cancer cells, XN induced apoptosis through upregulation of casp-3, casp-8, and casp-9 activation and downregulation in Bcl-2 expression [74].

Transcription factor specificity proteins (Sp), including Sp1, Sp3, and Sp4, are known to regulate survivin and are required for survival of tumor cells. Betulinic acid, a pentacyclic triterpene, was recently shown to decrease expression of survivin and induce apoptosis in LNCaP prostate cancer cells through targeted degradation of Sp proteins [75].

Some nutraceuticals have been shown to induce apoptosis through upregulation of DRs. Oleandrin sensitized lung cancer cells to TRAIL-induced apoptosis through upregulation of DR4 and DR5 [76]. We recently showed that garcinol can sensitize human colon cancer cells to TRAIL-induced apoptosis through induction of DR4 and DR5 [77]. Capsaicin was shown to sensitize malignant glioma cells to TRAIL-mediated apoptosis via DR5 upregulation and survivin downregulation [78]. Similarly, celastrol potentiated TRAIL-induced apoptosis through downregulation of cell survival proteins and upregulation of DR4 and DR5 in human breast cancer cells [79]. Enhancement in TRAIL-induced apoptosis was recently observed in human colon cancer cells by zerumbone. This was mediated through upregulation of DR4 and DR5 and generation of ROS [80]. In another study, zerumbone triggered apoptotic events independent of functional p53 in liver cancer cells through upregulation of Bax and downregulation of Bcl-2 [81].

Insulin-like growth factor I receptor (IGFIR) has emerged as a key therapeutic target in many human malignancies, including childhood cancers such as Ewing family tumors (EFT). EGCG was found to inhibit survival of EFT through inhibition of IGFIR activity, induction of apoptosis through upregulation of Bax, and decreased expression of Bcl-2, Bcl-XL, and myeloid cell leukemia

(Mcl)-1 proteins [82]. Induction of DNA damage and apoptosis in human ovarian cancer cells by genistein, a predominant isoflavone present in soybeans, was mediated through phosphorylation and activation of p53 and a decrease in the ratio of Bcl-2/Bax, Bcl-xL/Bax, and phosphorylated AKT levels [83]. Silymarin inhibited survival of hepatocellular carcinoma HepG2 cells by inducing apoptosis and facilitating cytochrome c release, upregulating proapoptotic proteins, and downregulating antiapoptotic proteins [84].

Some nutraceuticals have the potential to inhibit survival of tumor cells through mediation of the signal transducers and activators of transcription protein (STAT)-3 pathway. Muto et al. [85] showed that emodin can induce apoptosis in human myeloid cells through the elimination of Mcl-1. Emodin inhibited IL-6-induced activation of Janus-activated kinase 2 (JAK2) and phosphorylation of STAT-3; it also triggered casp-3 and casp-9 activation. Induction of apoptosis by emodin was almost abrogated in Mcl-1-overexpressing myeloma cells. These observations indicated that emodin can induce apoptosis in myeloid cells via downregulation of Mcl-1. Capsaicin has been reported to induce apoptosis in multiple myeloid cells through downregulation of STAT-3-regulated expression of Bcl-2, Bcl-xL, and survivin [86]. Adult T cell leukemia is an aggressive malignancy of peripheral T cells infected with human T cell leukemia virus type 1 (HTLV-1). Deguelin was shown to induce apoptosis in HTLV-1-transformed T cells via inhibition of survivin expression and STAT-3 phosphorylation through the ubiquitin/proteasome pathway [87]. In our laboratory, deguelin induced apoptosis in various cancer cells through the downregulation of antiapoptotic gene products [88].

Most nutraceuticals target by inhibiting NF- κ B activation, thereby inhibiting NF- κ B-regulated antiapoptotic proteins. Acetoxychavicol acetate inhibited cellular growth of multiple myeloma cells *in vivo* and *in vitro* through induction of apoptosis, activation of casp-8, inactivation of NF- κ B, and downregulation of antiapoptotic proteins [89]. Garcinol induced apoptosis in human breast cancer MCF-7 and MDA-MB-231 cells through caspase activation and downregulation of NF- κ B-regulated genes [90]. Plumbagin induced apoptosis with concomitant inactivation of Bcl-2 and the DNA binding activity of NF- κ B in breast cancer cells [91]. In non-small-cell lung cancer, plumbagin induced apoptosis through mediation of c-Jun N-terminal kinase (JNK) and the casp-3 pathway [92]. In addition, Murtaza et al. [93] demonstrated that fisetin can induce apoptosis in chemoresistant human pancreatic PaC AsPC-1 cells through suppression of DR3-mediated NF- κ B activation. Sulforaphane inhibited survival of orthotopically implanted PC-3 tumors through upregulation of DR4, DR5, Bax, and Bak and inhibition of NF- κ B, phosphoinositide 3-

kinase (PI3K)/AKT, and mitogen-activated protein kinase (MAPK)/ERK kinase (MEK) activation pathways [94].

We have identified a number of nutraceuticals from natural sources that target one or more steps in the NF- κ B activation pathway to sensitize and induce apoptosis in a variety of cancer cells. The most popular among these are acetoxychavicol acetate [95], evodiamine [96], noscapine [97], indirubin [98], isodeoxyelephantopin [99], anacardic acid [52], coronarin D [100], thymoquinone [101], γ -tocotrienol [102], β -escin [103], and withanolides [104].

3.2 Regulation of tumor cell proliferation by nutraceuticals

Dysregulated proliferation is one of the major characteristics of tumorigenesis. In normal cells, proliferation is regulated by a delicate balance between growth signals and antigrowth signals. Cancer cells, however, acquire the ability to generate their own growth signals and become insensitive to antigrowth signals [1]. Their growth is controlled by cell cycle regulators at the G1/S-phase boundary, in the S phase, and during the G2/M phases of the cell cycle. A precise set of proteins called cyclins and cyclin-dependent kinases (CDKs) control the progression of cell cycle events. Whereas cyclin binding is required for CDK activity, CDK inhibitors (CKIs) such as p21 and p27 prevent CDK activity and prevent cell cycle progression. The G1-to-S-phase transition also requires cellular v-myc myelocytomatosis viral oncogene homolog (c-Myc), and inhibition of c-Myc expression leads to growth arrest [105]. Deregulated expression of c-Myc has been implicated in a number of human malignancies [106, 107]. The expression of c-Myc in turn is regulated by cdc25, a phosphatase that activates CDKs.

The well-characterized tumor suppressor p53 has been implicated in controlling the G1-to-S-phase transition and in blocking cell cycle progression at the G1 phase in response to DNA damage [108]. A number of genes controlling cell cycle progression, including the CKI p21, are transcribed in a p53-dependent manner [109, 110]. Rb is a tumor suppressor retinoblastoma protein that, like p53, functions as a negative regulator of cell growth [111]. Rb inactivation or deletion has been found in many cancers, including retinoblastomas and carcinomas of the lung, breast, bladder, and prostate. By binding to and inhibiting transcription factors such as elongation 2 factor (E2F), which are necessary for S-phase entry, Rb is believed to inhibit cell cycle progression [112]. On the other hand, phosphorylation of Rb (pRb) by CDK/cyclin complexes results in the release of active E2F species to stimulate the transcription of genes involved in DNA synthesis and S-phase progression [113–115]. COX-2, an inducible prostaglandin endoperoxide synthase 2, has been linked with tumor cell proliferation. It can be rapidly induced by

growth factors, cytokines, and tumor promoters and is associated with inflammation [116–119]. Reports have demonstrated increased amounts of COX-2 in both premalignant and malignant tissues [120, 121].

Currently, a number of inhibitors based on cell cycle regulators, including nutraceuticals, are being developed as therapeutic intervention for cancer prevention. Nutraceuticals have been shown to have potential in cancer prevention for halting cell cycle progression by targeting one or more steps (Table 3) in the cell cycle. Most nutraceuticals prevent the transition of cancer cells from the G1 to S phase. Some of these nutraceuticals act through p53 and some through Rb. Acetyl-keto-beta-boswellic acid was shown to arrest colon cancer cells at the G1 phase, which was associated with decreases in cyclin-D1, cyclin-E, CDK-2, CDK-4, and pRb and an increase in p21 [122]. In Ehrlich ascites tumor cells, acetoxychavicol acetate was shown to stimulate the accumulation of tumor cells in the G1 phase of the cell cycle, which was accompanied by a decrease in pRb and an increase in Rb [123]. β -Escin, a triterpene saponin, induced cell cycle arrest at the G1/S phase by inducing p21 and reducing pRb in a p53-independent manner in HT-29 human colon cancer cells [124]. In gastric cancer cells, curcumin was shown to suppress the transition of cells from the G1 to S phase, which was accompanied by a decrease in cyclin-D1 and p21-activated kinase 1 activity [125].

Deguelin exhibited an antiproliferative effect in breast cancer cells by arresting cells at the S phase [126]. Emodin showed antiproliferative activity through a p53- and p21-dependent pathway and arrested liver cancer HepG2 cells in the G1 phase [127]. Fisetin was shown to arrest prostate cancer LNCaP cells at the G1 phase, which was associated with a decrease in cyclin-D1, cyclin-D2, and cyclin-E and their activating partners CDK-2, CDK-4, and CDK-6 and with the induction of p21 and p27 [128].

The effect of piceatannol on the proliferation of DU145 human prostate cancer cells was investigated. Piceatannol caused cells to accumulate in the G1 phase and was associated with a decrease in cyclin-A, cyclin-D1, CDK-2, and CDK-4 [129]. Another nutraceutical, silibinin, caused lung cancer cells to accumulate at the G1 phase, which correlated with decreased CDK-2 and CDK-4 activities [130]. Silymarin arrested hepatocellular carcinoma HepG2 cells at the G1 phase, concomitant to a reduction in β -catenin, cyclin-D1, c-Myc, and proliferating cell nuclear antigen [84]. Thymoquinone, a component of *Nigella sativa*, was shown to abrogate the progression of prostate cancer cells from the G1 to S phase. These effects correlated with upregulation in p21 and p27 and downregulation in androgen receptor and E2F-1 [131]. Quercetin also induced cell cycle arrest at the G1 phase by elevating p53, p21, and p27 in a human hepatoma cell line *in vitro*

[132]. Sulforaphane was shown to suppress proliferation of epithelial ovarian cancer cells through G1 cell cycle arrest, reduction in pRb and free E2F-1, and increase in Rb [133].

Some nutraceuticals prevent tumor cell proliferation by preventing transitions from the G2 to M phase. Butein was shown to inhibit cell growth in human hepatoma cancer cell lines—HepG2 and Hep3B—by inducing G2/M phase arrest. This inhibition in cell growth was associated with increased phosphorylation of ataxia telangiectasia mutated (ATM), checkpoint kinase (Chk)-1, and Chk-2, and reduction in cell division cycle 25 homolog c (cdc25c) levels. The inhibition in cell growth was also correlated with ROS generation and JNK activation [134]. Celastrol was shown to inhibit cell proliferation in C6 glioma cells by arresting the cells at the G2/M phase through upregulation of p21 and p27 and downregulation of CDK-2 [135]. Evodiamine exhibited antiproliferative activity by arresting human thyroid ARO cancer cells at the G2/M phase, which was associated with decreased expression of cdc2-p15 [136].

Recently, an ataxia telangiectasia and Rad3-related protein—Chk-1-mediated DNA damage response was shown to trigger p53/p21 activation and G2/M arrest in HepG2 and A549 cells in response to gambogic acid treatment [137]. Betulinic acid evoked an increase in the G2/M phase population and a decrease in the S-phase population in human gastric adenocarcinoma cells. This correlated with a decrease in Hiwi and its downstream target cyclin-B1 [138]. Zerumbone was shown to suppress proliferation of leukemic NB4 cells by inducing G2/M cell cycle arrest, decreasing cyclin-B1 expression, and phosphorylating ATM/Chk-1/Chk-2 and cdc25c [139].

Berberine exhibited antiproliferative activity against human osteosarcoma cells by inducing cell cycle arrest at the G1 and G2/M phases. Whereas induction of G1 arrest was accompanied by p53-dependent upregulation of p21, G2/M arrest occurred regardless of p53 status [140]. Guggulsterone was shown to suppress the proliferation of cancer cells through inhibition of DNA synthesis and induction of cell cycle arrest in the S phase; these effects were mediated through downregulation of cyclin-D1 and cdc2 and upregulation of p21 and p27 [141].

NF- κ B has been shown to bind to the promoter of genes involved in cellular proliferation. A few nutraceuticals target one or more steps in NF- κ B activation to regulate tumor cell proliferation. With use of an orthotopic murine model of ovarian cancer, curcumin was shown to inhibit tumor growth that correlated with inhibition in NF- κ B and a STAT-3 activation pathway [142]. In another study, curcumin exhibited antiproliferative activity in association with decreased expression of cyclin-D1 and CDK-4 in breast cancer cell lines MDA-MB-231 and BT-483 [143]. Fisetin, a naturally occurring flavonoid, was shown to

Table 3 Effect of nutraceuticals on tumor cell proliferation

Nutraceuticals	Effect
ACA	Induced accumulation of tumor cells in the G1 phase, decreased pRb in EATC [123]
AKBA	Arrested colon cancer cells at the G1 phase by decreasing cyclin-D1, cyclin-E, CDK-2, CDK-4, pRb, and increasing p21 [122]
Anacardic acid	Downregulated NF- κ B-dependent expression of cyclin-D1, COX-2, and c-Myc [52]
Berberine	Exhibited antiproliferative activity against human osteosarcoma cells by inducing cell cycle arrest at G1 and G2/M phase and p53-dependent upregulation of p21 [140]
β -Escin	Induced cell cycle arrest at the G1/S phase by inducing p21 and reducing pRb independent of p53 in HT-29 cells [124]
Betulinic acid	Evoked G2/M cell cycle arrest associated with a decrease in Hiwi and cyclin-B1 in human gastric adenocarcinoma cells [138]
Butein	Inhibited cell growth in HepG2 and Hep3B through G2/M phase arrest, phosphorylation of ATM and Chk-1/2, and reduction in cdc25c [134]
Capsaicin	Decreased the expression of E2F-responsive cyclin-E, thymidylate synthase, cdc25A, and cdc6 in SCLC [150]
Celastrol	Inhibited cell proliferation in C6 glioma cells by inducing G2/M phase arrest through upregulation of p21 and p27 and downregulation of CDK-2 [135]
Coronarin	Suppressed NF- κ B-dependent expression of cyclin-D1, c-Myc, and COX-2 [100]
Curcumin	Suppressed G1/S-phase transition accompanied with a decrease in cyclin-D1 and PAK1 activity in gastric cancer cells [125]
Deguelin	Exhibited antiproliferative effect in breast cancer cells by arresting cells at the S phase [126]
Diosgenin	Inhibited proliferation through downregulation of IKK activation and expression of cyclin-D1, c-Myc, and COX-2 [145]
Emodin	Exhibited antiproliferative activity through p53- and p21-dependent G1-phase arrest in HepG2 cells [127]
Evodiamine	Arrested human thyroid ARO cancer cells at G2/M phase concomitant with a decrease in cdc2 expression [136]
Fisetin	Arrested LNCaP cells at G1 phase; decreased cyclin-D1, cyclin-D2, cyclin-E, CDK-2, CDK-4, and CDK-6; induced p21 and p27 [128]
Flavopiridol	Inhibited TNF-induced c-Myc expression through inhibition of NF- κ B activation in various cancer cells [61]
Gambogic acid	Induced G2/M arrest in HepG2 and A549 cells through ATR/Chk-1-mediated p53/p21 activation [137]
Genistein	Inhibited growth of TRAMP cancer cells; repressed cyclin-B1; activated p21 through mediation of Myt-1 and Wee-1 kinases [164]
Gossypol	Arrested MAT-LyLu prostate cancer cells at G0/G1 phase; downregulated cyclin-D1, CDK-4, and pRb through modulation of TGF- β -1 and AKT signaling [151]
Guggulsterone	Suppressed proliferation of cancer cells through cell cycle arrest in S phase; downregulated cyclin-D1 and cdc2 and upregulated p21 and p27 [35]
Isodeoxyelephantopin	Inhibited proliferation through downregulation of NF- κ B-regulated cyclin-D1, c-Myc, and COX-2 [99]
Morin	Suppressed NF- κ B-regulated cyclin-D1 and COX-2 [146]
Noscapine	Inhibited proliferation of leukemic cells through suppression of NF- κ B-regulated cyclin-D1 and COX-2 [97]
Piceatannol	Accumulated DU145 human prostate cancer cells in G1 phase; decreased expression of cyclin-A, cyclin-D1, CDK-2, and CDK-4 [129]
Pinitol	Suppressed NF- κ B-dependent cyclin-D1 and COX-2 expression [147]
Quercetin	Induced cell cycle arrest at G1 phase, elevated p53, p21, and p27 in human hepatoma cell line [132]
Silibinin	Accumulated lung cancer cells at G1 phase; decreased activity of CDK-2 and CDK-4 [130]
Sulforaphane	Suppressed proliferation of EOC through G1 cell cycle arrest, reduction in pRb and free E2F-1, and upregulation in Rb [133]
Thymoquinone	Abrogated the progression of prostate cancer cells from G1 to S phase; upregulated p21 and p27; downregulated AR and E2F-1 [131]
Ursolic acid	Downregulated COX-2 and cyclin-D1 in nonspecific cell types [148]

Table 3 (continued)

Nutraceuticals	Effect
Tubocapsanolide A	Induced G1 growth arrest in human lung cancer cells; inhibited binding of Rel A subunit of NF- κ B to Skp2; upregulated p21 and p27 [149]
Zerumbone	Suppressed proliferation of leukemic NB4 cells by inducing G2/M cell cycle arrest, decreasing cyclin-B1 expression, and phosphorylating ATM/Chk-1/2 and cdc25c [139]

ACA acetoxychavicol acetate, *AKBA* acetyl-11-keto-beta-boswellic acid, *AKT* AKT8 virus oncogene cellular homolog, *AR* androgen receptor, *ATM* ataxia telangiectasia mutated, *ATR* ataxia telangiectasia and Rad3-related protein, *cdc25c* cell division cycle 25 homolog C (*S. pombe*), *CDK* cyclin-dependent kinase, *Chk* checkpoint kinase, *c-Myc* cellular v-myc myelocytomatosis viral oncogene homolog (avian), *COX-2* cyclooxygenase 2, *EATC* Ehrlich ascites tumor cell, *E2F* elongation 2 factor, *EGFR* epidermal growth factor receptor, *ERK* extracellular signal-regulated kinase, *EOC* epithelial ovarian cancer cells, *IKK* I κ B kinase, *JNK* c-Jun N-terminal kinase, *Myt-1* myelin transcription factor 1, *NF- κ B* nuclear factor kappa B, *PAK1* p21-activated kinase 1, *pRb* phosphorylated retinoblastoma, *Rb* retinoblastoma protein, *SCLC* small-cell lung cancer, *Skp2* S-phase kinase-associated protein 2, *STAT* signal transducer and activator of transcription, *TNF* tumor necrosis factor, *TGF- β* transforming growth factor β , *TRAMP* transgenic adenocarcinoma of mouse prostate model

downregulate COX-2 expression and to inhibit prostaglandin E2 secretion in HT29 human colon cancer cells; this correlated with decreased activity in wnt signaling through downregulation of β -catenin, inhibition in epidermal growth factor receptor activity, activation of NF- κ B, and subsequent decrease in cyclin-D1 expression [144].

We have identified a number of nutraceuticals with the potential to inhibit proliferation of cancer cells through inhibition of the NF- κ B activation pathway and NF- κ B-dependent gene products involved in proliferation such as c-Myc, COX-2, and cyclin-D1. Some of these nutraceuticals are flavopiridol [61], anacardic acid [52], coronarin D [100], diosgenin [145], isodeoxyelephantopin [99], morin [146], noscapine [97], pinitol [147], and ursolic acid [148].

S-phase kinase-associated protein 2 (Skp2), an F-box protein with an NF- κ B binding site in its promoter, has been implicated in the degradation of p21 and p27. Recently, Tubocapsanolide A, a bioactive withanolide, was shown to induce G1 growth arrest in A549, H358, and H226 human lung cancer cells. The antiproliferative effects of Tubocapsanolide A were mediated through inhibition of binding of the RelA subunit of NF- κ B to Skp2, inhibition of Skp2 expression, and upregulation of p21 and p27 [149].

The antiproliferative activity of capsaicin correlated with decreased expression of E2F-responsive proliferative genes such as cyclin-E, thymidylate synthase, cdc25A, and cdc6 in small-cell lung cancer [150]. Gossypol was shown to inhibit the growth of MAT-LyLu prostate cancer cells by arresting the cells at the G0/G1 phase and downregulating cyclin-D1, CDK-4, and pRb expression. These effects of gossypol were associated with modulation of transforming growth factor β -1 and AKT signaling [151].

Genistein has been shown to inhibit the growth of several cancer cells [152–157]. In breast cancer and melanoma cells, genistein induced G2/M cell cycle arrest

[157, 158]. Although most studies indicated that genistein causes G2/M arrest, some showed that genistein could also arrest mouse fibroblast and melanoma cells at the G0/G1 phase of the cell cycle [159]. In addition, genistein was shown to halt cell growth by upregulating p21 in various cancer cells [160–163]. Touny and Banerjee [164] reported the involvement of upstream kinases myelin transcription factor 1 (Myt-1) and Wee-1 in the transcriptional repression of cyclin-B1 and activation of p21 in prostate cancer cells. They found that genistein treatment increased Myt-1 levels and decreased Wee-1 phosphorylation, providing new insight into the possible mechanism of genistein-induced G2/M arrest.

3.3 Regulation of tumor cell invasion by nutraceuticals

Tumor cell invasion and metastasis are interrelated processes involving cell growth, cell adhesion, cell migration, and proteolytic degradation of tissue barriers such as the extracellular matrix and basement membrane. Several proteolytic enzymes, including MMPs (chiefly MMP-2 and MMP-9) [165, 166] and intercellular adhesion molecule (ICAM; chiefly ICAM-1), participate in the degradation of these barriers [167, 168]. A number of studies in lung, colon, breast, and pancreatic carcinomas have demonstrated overexpression of MMPs in malignant tissues compared with adjacent normal tissues [169–176]. Apart from MMPs, cysteine proteases [177] and serine proteases [178] such as urokinase-type plasminogen activator (u-PA) have also been involved in the invasion and metastasis of cancer cells. Since both u-PA and u-PA receptor (u-PAR) contain binding sites for NF- κ B and activator protein (AP)-1 in their promoter regions [179–181], inhibition of these transcription factors will eventually result in the inhibition of u-PA–u-PAR complex and subsequent suppression of invasive behavior.

A wide variety of nutraceuticals derived from natural sources has been shown to inhibit tumor cell invasion and metastasis by targeting one or more molecules (Table 4). Allicin inhibited TNF- α -induced ICAM-1 expression in human umbilical endothelial cells (ECs) [182]. *S*-Allylcysteine and *S*-allylmercaptocysteine, obtained from garlic, suppressed the invasion ability of androgen-independent invasive prostate cancer cells [183] through restoration of E-cadherin expression. Allyl isothiocyanate (AITC) suppressed MMP-2 and MMP-9 at both protein and mRNA levels in human hepatoma SK-Hep1 cells *in vitro* [184]. Apigenin plays an important role in inhibiting the adhesion and motility of breast cancer cells through mediation of the HER2–HER3–PI3K–AKT pathway [185]. Apigenin inhibited metastasis of lung melanoma cells by inhibiting vascular cell adhesion molecule 1 (VCAM-1) expression in a dose-dependent manner [186].

Ezrin is highly expressed in metastatic tumors and is involved in filopodia formation as well as promotion of tumor metastasis. Berberine, an alkaloid, was recently shown to inhibit invasion and motility in nasopharyngeal carcinoma cell line 5-8F through repression of ezrin phosphorylation at Thr⁵⁶⁷ by Rho kinase and inhibition in filopodia formation [187]. Berberine has also been reported to suppress *in vitro* migration and invasion of human SCC-4 tongue squamous cancer cells through inhibition of FAK, IKK, NF- κ B, u-PA, and MMP-2 and MMP-9 [59].

Increasing evidence has shown that epithelial–mesenchymal transition plays a critical role in tumor cell metastasis. Butein, a polyphenolic compound obtained from stem bark of cashews, was recently shown to inhibit migration and invasion through the ERK-1/ERK-2 and NF- κ B signaling pathways in human bladder cancer cells. The inhibitory effect of butein was associated with the reversal of epithelial–mesenchymal transition [188]. We have shown that butein can inhibit TNF- α -induced invasion in human lung adenocarcinoma H1299 cells, which was associated with inhibition in NF- κ B activation and downregulation in MMP-9 [189].

Caffeic acid had a strong inhibitory effect on MMP-9 activity in nonspecific cell types *in vitro* [190]. Capsaicin significantly inhibited the migration of highly metastatic B16-F10 melanoma cells through inhibition of the PI3K/AKT/rat sarcoma (Ras)-related C3 botulinum toxin substrate 1 signaling pathway [191]. Carnosol reduced MMP-9 levels in mouse melanoma cells *in vitro* through downregulation of NF- κ B and AP-1 [192]. β -Carotene inhibited the invasion of rat ascites hepatoma AH109A cells in a dose-dependent manner by acting as ROS quenchers [193]. Catechin gallate, a phenolic compound obtained from the red pine, inhibited the invasion and migration of SK-Hep-1 human hepatocellular carcinoma cells, which strongly correlated with reduced expression of MMP-2 and MMP-

9 [194]. Celastrol, a quinone methide triterpene from the medicinal plant *Tripterygium wilfordii*, exerted potent antimetastatic activity both *in vitro* and *in vivo* [195] through p38 MAPK, suppression of β -1 integrin ligand affinity, focal adhesion formation, reduced phosphorylation of FAK, and inhibition of cell–extracellular matrix adhesion of human lung cancer 95-D and mouse melanoma B16-F10 cells. Crocetin was shown to suppress ICAM-1 and MMPs in bovine endothelial cells [196].

Curcumin exerted a dose- and time-dependent inhibitory effect on the invasion and migration of mouse–rat hybrid retina ganglion cells (N18) *in vitro* [197]. This inhibited invasion was associated with downregulation of PKC, FAK, NF- κ B p65, Rho A, MMP-2, and MMP-9. In Hep2 human laryngeal cancer cells, curcumin inhibited tumor cell invasion and metastasis that were associated with down-regulated MMP-2 expression and reduced activity and expression of integrin receptors, FAK, and membrane-type 1 MMP [198]. Diallyl disulfide inhibited the activation of MMP-2 and MMP-9 in human umbilical vein endothelial cells (HUVECs) *in vitro* [199].

The chemokine receptor CXCR4, with its unique ligand CXC chemokine ligand 12 (CXCL12), is required for metastasis of breast cancer cells [200, 201]. 3, 3'-Diindolylmethane showed antimetastatic ability in MCF-7 and MDA-MB-231 breast cancer cells by lowering CXCR4 and CXCL12 levels [200, 201]. With the use of androgen-insensitive prostate cancer (DU-145) cells, Vayalil and Katiyar [202] showed that EGCG can inhibit fibroblast-conditioned medium-induced production of pro and active forms of MMP-2 and MMP-9. Nuclear localization of NF- κ B, as well as MMP-9 expression and invasion, was suppressed in lung carcinoma cells treated with EGCG [203].

Takada et al. [96] recently showed that evodiamine can inhibit TNF-induced invasion in human lung adenocarcinoma H1299 cells through inhibition in NF- κ B activation and downregulation in MMP-9. The antimetastatic potential of fisetin was mediated through inhibition of phosphorylation of ERK-1/ERK-2 and downregulation in expression of MMP-2 and u-PA in A549 cells [204].

c-erbB-2 is a key molecule for breast cancer metastasis, and overexpression of *c-erbB-2* has been correlated with increased MMP secretion and metastatic potential in breast cancer cells [205]. Flavopiridol was found to inhibit the secretion of MMP-2 and MMP-9 in the breast cancer cells. Inhibition in MMP secretion was associated with significant downregulation of *c-erbB-2* and inhibition of cell invasion [206]. Ganoderic acids isolated from *Ganoderma lucidum* suppressed invasive behavior of breast cancer cells by inhibiting AP-1 and NF- κ B activity, resulting in inhibition of u-PA secretion [207]. Genistein inhibited cell adhesion to vitronectin and cell migration of invasive breast cancer cells

Table 4 Effect of nutraceuticals on tumor cell invasion

Nutraceuticals	Effect
Allicin	Inhibited TNF- α -induced ICAM-1 expression in HUVECs [182]
S-Allylcysteine, AITC	Suppressed the invasion of androgen-independent invasive PCa cells by restoration of E-cadherin expression [183]
Apigenin	Downregulated MMP-2/9 activity in human hepatoma SK-Hep1 cells [184]
Berberine	Inhibited metastasis of lung melanoma cells by inhibiting VCAM-1 expression [186]
Butein	Suppressed <i>in vitro</i> migration and invasion of human SCC-4 tongue squamous cancer cells through inhibition of FAK, IKK, NF- κ B, u-PA, and MMP-2/9 [59]
Butein	Inhibited migration and invasion in human bladder cancer cells through the ERK-1/2 and NF- κ B signaling pathways [188]
Caffeic acid	Inhibited MMP-9 activity in human hepatocellular carcinoma cell line [190]
Capsaicin	Inhibited the migration of a highly metastatic B16-F10 melanoma cells through the inhibition of the PI3K/AKT/Rac1 signaling pathway [191]
Carnosol	Suppressed expression and activation of MMP-9 in mouse melanoma B16-F10 cells [192]
β -Carotene	Inhibited the invasion of rat ascites hepatoma AH109A cells by acting as ROS quenchers [193]
Catechin gallate	Inhibited the invasion and migration of SK-Hep-1 human hepatocellular carcinoma cells by reducing the expression of MMP-2 and -9 [194]
Celastrol	Inhibited metastasis in human lung cancer 95-D and mouse melanoma B16-F10 cells through mediation of p38 MAPK and reduced phosphorylation of FAK [195]
Crocetin	Suppressed glycation end-product-induced ICAM-1 expression in bovine ECs [196]
Curcumin	Downregulated MMP-2 expression and activity and expression of integrin receptors, FAK, and MT1-MMP in Hep2 cells [198]
Diallyl disulfide	Inhibited MMP-2 and MMP-9 activity in HUVECs [199]
3,3'-Diindolylmethane	Inhibited metastasis of breast cancer (MDA-MB-231) and ovarian cancer (BG-1) cells by lowering the level of CXCR4 and CXCL12 [200, 201]
EGCG	Suppressed invasion in lung carcinoma cells by preventing nuclear localization of NF- κ B and downregulating MMP-9 expression [203]
Evodiamine	Inhibited TNF-induced invasion in human lung adenocarcinoma H1299 cells associated with inhibition in NF- κ B activation and downregulation in MMP-9 expression [96]
Fisetin	Inhibited metastasis in human lung adenocarcinoma A549 cells through inhibition of phosphorylation of ERK-1/2 and downregulation in the expressions of MMP-2 and u-PA [204]
Flavopiridol	Inhibited cell invasion in MDA-MB-435 cells by inhibiting secretion of MMP-2/9 and downregulation of c-erbB-2 [206]
Ganoderic acid	Suppressed invasion of breast cancer cells by inhibiting AP-1 and NF- κ B activity and u-PA secretion [207]
Genistein	Inhibited cell adhesion to vitronectin and cell migration of invasive breast cancer cells by inhibiting the transcriptional activity of AP-1 and NF- κ B [208]
[6]-Gingerol	Suppressed expression and enzymatic activity of MMP-2/9 in human breast cancer cells [209].
Indole-3-carbinol	Inhibited 17- β -estradiol-stimulated migration and invasion in MCF-7 cells associated with an increase in E-cadherin and α -, β -, and γ -catenin [210]
Kaempferol	Inhibited TNF- α -induced ICAM-1 expression [270]
Lycopene	Suppressed migration and invasion of hepatoma cell line, SK-Hep-1 by upregulating metastasis suppressor gene nm23-H1 [211]
Myricetin	Inhibited expression and activity of MMP-2 in colorectal cancer cells [212]
Piperine	Inhibited the MMP production in B16-F10 melanoma cells [213]
Quercetin	Decreased MMP-2 and MMP-9 expression in PC-3 cells [214]
Resveratrol	Inhibited HO-1-mediated NF- κ B activation and MMP-9 and MMP-2 expression in A549 cells [215]
Sanguinarine	Inhibited invasiveness of human breast carcinoma MDA-MB-231 cells by decreasing activities of MMP-2 and MMP-9 [279]
Silibinin	Inhibited invasion and motility of SCC-4 tongue cancer and A459 lung cancer cells by downregulating MMP-2 and u-PA and upregulating TIMP-2 expression [216]
Sulforaphane	Inhibited the activation of MMPs and lung metastasis induced by melanoma cells in mice [219]
γ -Tocotrienol	Inhibited metastasis in gastric adenocarcinoma SGC-7901 cells that correlated with a decrease in MMP-2/9 expression and upregulation of TIMP-1 and TIMP-2 [220]

Table 4 (continued)

Nutraceuticals	Effect
Ursolic acid	Downregulated MMP-9 in HT1080 human fibrosarcoma cells [280]; inhibited IL-1 β or TNF- α -induced rat C6 glioma cell invasion through downregulation of NF- κ B activation and MMP-9 expression [221]
Vanillin	Inhibited invasion and migration of cancer cells that correlated with an inhibition in MMP-9 activity [260]
Zerumbone	Suppressed TNF-induced tumor cell invasion associated with an inhibition in NF- κ B activation and MMP-9 expression [223]

AITC allyl isothiocyanate, *AKT* AKT8 virus oncogene cellular homolog, *AP-1* activator protein 1, *CXCL12* CXC chemokine ligand 12, *CXCR4* CXC chemokine receptor 4, *ECs* endothelial cells, *EGCG* epigallocatechin-3-gallate, *ERK* extracellular signal-regulated kinase, *FAK* focal adhesion kinase, *HO-1* heme oxygenase 1, *HUVECs* human umbilical vein endothelial cells, *ICAM-1* intercellular adhesion molecule 1, *IKK* I κ B kinase, *IL-1 β* interleukin 1 β , *MAPK* mitogen-activated protein kinase, *MMP* matrix metalloproteinase, *MT1-MMP* membrane-type 1 matrix metalloproteinase, *NF- κ B* nuclear factor kappa B, *PCa* prostate cancer, *PI3K* phosphoinositide 3 kinase, *ROS* reactive oxygen species, *TIMP-2* tissue inhibitor of metalloproteinase 2, *TNF- α* tumor necrosis factor α , *u-PA* urokinase-type plasminogen activator, *VCAM-1* vascular cell adhesion molecule 1

by inhibiting the transcriptional activity of AP-1 and NF- κ B, resulting in the suppression of u-PA secretion from cancer cells [208]. [6]-Gingerol inhibited cell adhesion, invasion, motility, and activities of MMP-2 and MMP-9 in human breast cancer cell lines *in vitro* [209]. Indole-3-carbinol suppressed the 17- β -estradiol-stimulated migration and invasion in estrogen-responsive MCF-7 cells. The suppressed invasion was associated with an increase in invasion suppressor molecules, E-cadherin, and α -, β -, and γ -catenin [210].

Lycopene, a dietary constituent present in tomatoes, red fruits, and vegetables, was recently shown to suppress migration and invasion of hepatoma cell line SK-Hep-1, which was associated with upregulation of a metastasis suppressor gene, nm23-H1 [211]. Myricetin inhibited MMP-2 expression and enzyme activity in colorectal carcinoma cells *in vitro* [212]. Piperine inhibited MMP production in melanoma cells *in vitro*, preventing collagen matrix invasion in a dose-dependent manner [213]. Quercetin decreased expression of MMP-2 and MMP-9 in a dose-dependent manner in PC-3 prostate cancer cells *in vitro* [214]. Resveratrol reduced the migratory and invasive abilities of A549 lung cancer cells and was associated with inhibition of NF- κ B activation and expression of MMP-2 and MMP-9 [215]. Sanguinarine inhibited invasiveness of MDA-MB-231 human breast carcinoma cells by decreasing the activities of MMP-2 and MMP-9 [67]. Silibinin, a flavonolignan, inhibited invasion and motility of SCC-4 tongue cancer and A459 lung cancer cells by downregulating MMP-2 and u-PA and upregulating tissue inhibitor of metalloproteinase (TIMP)-2 and PAI-1 expression [216, 217]. Recently, Lee et al. [218] reported that silibinin reduced PMA-induced invasion of MCF-7 cells through specific inhibition of AP-1-dependent MMP-9 expression. Sulforaphane inhibited the activation of MMPs, thereby inhibiting lung metastasis induced by melanoma cells in mice [219].

The invasion and metastatic capacities of SGC-7901 gastric adenocarcinoma cells and their correlation with antimetastatic mechanisms induced by γ -tocotrienol were explored. Cell attachment was decreased by the γ -tocotrienol, which was associated with decreased MMP-2 and MMP-9 expression and upregulation of TIMP-1 and TIMP-2 [220]. Ursolic acid has been reported to reduce IL-1 β - or TNF- α -induced rat C6 glioma cell invasion through downregulation of NF- κ B activation and MMP-9 expression [221]. Zerumbone downregulated expression of CXCR4 on HER2-overexpressing breast cancer cells in a dose- and time-dependent manner. Suppression of CXCR4 expression by zerumbone correlated with the inhibition of CXCL12-induced invasion of both breast and pancreatic cancer cells [222]. In another study, zerumbone suppressed TNF-induced NF- κ B activation and NF- κ B-mediated MMP-9 expression that correlated with inhibition in tumor cell invasion [223].

3.4 Regulation of tumor cell angiogenesis by nutraceuticals

Angiogenesis, the process during which new blood vessels are formed from preexisting ones, can be classified as either physiological or pathological. Physiological angiogenesis provides a driving force for organ development in ontogeny, is necessary for ovulation, and is a prerequisite for wound healing; pathological angiogenesis occurs during tumor growth at primary and metastatic sites [224]. The angiogenic cascade during tumor development consists of the release of angiogenic factors, binding of angiogenic factors to receptors on ECs, EC activation, degradation of the basement membrane by proteases, and migration and proliferation of ECs. Adhesion molecules then help to pull the sprouting blood vessels forward, and ECs are finally organized into a network of new blood vessels [225]. The signaling pathway governing tumor angiogenesis is exceedingly complex, involving various angiogenic mediators.

The major signaling mediators include VEGF, platelet-derived growth factor, fibroblast growth factors (FGFs), epidermal growth factor, ephrins, angiopoietins, endothelins, integrins, cadherins, and notch [226].

Since the role of angiogenesis in tumor development was first revealed [227], a number of antiangiogenic compounds have been developed, including bevacizumab (Avastin), sunitinib (SUTENT), sorafenib (Nexavar), cediranib maleate (Recentin), and pazopanib [226]. Many nutraceuticals have shown angiogenesis-modulating properties by targeting one or more steps in the signaling pathway (Table 5).

Alliin showed potential to inhibit FGF-2-induced human EC tube formation and angiogenesis in a chick chorioallantoic membrane (CAM) model. Alliin also inhibited VEGF-induced angiogenesis in the CAM model [228]. In a C57BL/6 mouse model bearing B16-F10 melanoma cells, AITC inhibited NO synthesis and TNF- α production, which correlated with inhibited angiogenesis [229]. Recently, the antiangiogenic effect of AITC was investigated in Swiss albino mice into which Ehrlich ascites tumor cells were transplanted [230]. AITC significantly reduced vessel sprouting and exhibited potent antiangiogenic activity that was associated with significant reduction in VEGF expression.

Fang et al. [231] showed that apigenin can inhibit expression of hypoxia-inducible factor 1 (HIF-1) and VEGF in various types of cancer cells under normoxic and hypoxic conditions; this inhibition was associated with significant inhibition in tumor angiogenesis. In another study, caffeic acid suppressed STAT-3-mediated HIF-1 and VEGF expression, which correlated with inhibited vascularization and angiogenesis in mice bearing Caki-I human renal carcinoma cells [232].

Capsaicin has been shown to inhibit *in vitro* and *in vivo* angiogenesis. *In vitro*, capsaicin inhibited VEGF-induced capillary-like tube formation of primary cultured human ECs. It also inhibited VEGF-induced vessel sprouting in a rat aortic ring assay, VEGF-induced vessel formation in a mouse Matrigel plug assay, and VEGF-induced p38 MAPK, p125 (FAK), and AKT activation [233].

Curcumin was found to completely prevent induction of VEGF synthesis in microvascular ECs stimulated with glycation end products, which was mediated by downregulation of NF- κ B and AP-1 activity [234]. Curcumin also inhibited angiogenesis through mediation of angiopoietins 1 and 2, HIF-1, and heme oxygenase 1 in cancer cells [235].

Diallyl sulfide reduced the serum level of VEGF in C57BL/6 mice bearing B16-F10 melanoma cells [199]. EGCG inhibited production of VEGF and IL-8 from normal human keratinocytes [236–238]. In human colon cancer cells, EGCG attenuated VEGF production through inhibition of ERK-1 and ERK-2 kinases [239]. Recently, EGCG

inhibited ephrin-A1-mediated EC migration as well as tumor angiogenesis through inhibition in ERK-1/ERK-2 activation [240].

Flavopiridol decreased hypoxia-mediated HIF-1 α expression, VEGF secretion, and tumor cell migration in human U87MG and T98G glioma cell lines [241]. These *in vitro* data were correlated with reduced vascularity of intracranial syngeneic GL261 gliomas in animals treated with flavopiridol. Gambogic acid inhibited activation of VEGF receptor 2 and of downstream kinases such as c-Src, FAK, and AKT and inhibited angiogenesis in HUVECs and human prostate cancer cells (PC3) [242]. Genistein suppressed VEGF and FGF-2 expression and inhibited tyrosine kinase phosphorylation and activation of AKT and NF- κ B, resulting in inhibition of angiogenesis in renal cell carcinoma [243–246]. [6]-Gingerol, in response to VEGF, blocked capillary-like tube formation and strongly inhibited both sprouting of ECs in rat aorta and formation of new blood vessels in mouse cornea [247].

Luteolin inhibited VEGF-induced survival and proliferation of HUVECs through PI3K/AKT-dependent pathways [248]. Perillyl alcohol decreased the release of VEGF from cancer cells and stimulated expression of Ang2 by ECs, indicating that it might suppress neovascularization and induce vessel regression [249]. In another study, quercetin inhibited hypoxia-induced VEGF expression in NCI-H157 cells, which correlated with suppression in STAT-3 tyrosine phosphorylation, suggesting that inhibition of STAT-3 function may play a role in angiogenesis inhibition [250].

Resveratrol is able to suppress the growth of new blood vessels in animals. It directly inhibits capillary endothelial cell growth and blocks both VEGF- and FGF-receptor-mediated angiogenic responses through inhibition of phosphorylation of MAPK in ECs [251]. Rosmarinic acid (RA), a water-soluble polyphenolic compound, reduced the intracellular ROS level, H₂O₂-dependent VEGF expression, and IL-8 release of ECs. These activities were related to the antiangiogenic potential of RA [252]. Sanguinarine exhibited antiangiogenic activity by directly suppressing the proliferative effect of VEGF on ECs; this effect was mediated through downregulation of VEGF-induced AKT activation [253].

The *in vivo* efficacy of silibinin against human colorectal carcinoma HT29 xenograft growth in mice was investigated recently. Silibinin administration was associated with antiangiogenic activities in nude mice, resulting in downregulation of nitric oxide synthase, COX, HIF-1 α , and VEGF expression [254]. In human prostate cancer cells, sulforaphane inhibited NF- κ B-regulated VEGF expression *in vitro* [255]. In HUVECs, sulforaphane inhibited angiogenesis through activation of forkhead homeobox type O transcription factors and inhibition of MEK/ERK and PI3K/AKT pathways [256]. In human leukemic cell lines, taxol, obtained from the bark of *Taxus brevifolia*, showed

Table 5 Effect of nutraceuticals on tumor cell angiogenesis

Nutraceuticals	Effect
Alliin	Inhibited FGF2 and VEGF secretion from human fibrosarcoma cells. Inhibited FGF2-induced EC tube formation and angiogenesis in a CAM model [228]
AITC	Exhibited potent antiangiogenic activity associated with a significant reduction in VEGF expression in a mice model bearing EAT cells [230]
Apigenin	Inhibited expression of HIF-1 and VEGF in cancer cells associated with a significant inhibition in tumor angiogenesis [225]
Caffeic acid	Suppressed STAT-3-mediated expression of HIF-1 and VEGF, inhibited vascularization and angiogenesis in mice bearing Caki-I human renal carcinoma cell line [232]
Capsaicin	Inhibited VEGF-induced p38 MAPK, p125 (FAK), and AKT activation, and capillary-like tube formation in human ECs [233]
Curcumin	Inhibited induction of VEGF synthesis in microvascular ECs through downregulation of NF- κ B and AP-1 activity [234]
Diallyl sulfide	Reduced serum level of VEGF in B16-F10 melanoma bearing C57BL/6 mice [199]
EGCG	Inhibited VEGF production through inhibition of ERK-1 and ERK-2 kinases in human colon cancer cells [239]
Flavopiridol	Inhibited hypoxia-mediated HIF-1 α expression, VEGF secretion, and tumor cell migration in human U87MG and T98G glioma cell lines [241]
Gambogic acid	Inhibited activation of VEGFR2, c-Src, FAK, and AKT and angiogenesis in HUVEC and human prostate cancer cells (PC3) [242]
Genistein	Suppressed VEGF and FGF-2 expression; inhibited tyrosine kinase and activation of NF- κ B and AKT; inhibited angiogenesis in renal cell carcinoma [245]
[6]-Gingerol	Inhibited VEGF-induced capillary-like tube formation and sprouting in ECs in the rat aorta and new blood vessel formation in the mouse cornea [247]
Luteolin	Inhibited VEGF-induced survival and proliferation of HUVECs through PI3K/AKT-dependent pathways [248]
Perillyl alcohol	Decreased VEGF release from cancer cells and stimulated the expression of Ang2 by ECs [249]
Quercetin	Inhibited hypoxia-induced VEGF expression in NCI-H157 cells through suppression of STAT-3 tyrosine phosphorylation [250]
Resveratrol	Blocks VEGF- and FGF-receptor-mediated angiogenic responses through inhibition of MAPK phosphorylation in ECs [251]
Rosmarinic acid	Inhibited angiogenesis, VEGF expression, and IL-8 release in ECs [252]
Sanguinarine	Exhibited antiangiogenic activity through suppression of VEGF-induced proliferation and AKT activation in EC [253]
Silibinin	Exhibited antiangiogenic activities against human CRC HT29 xenograft growth in mice associated with downregulation of NOS, COX, HIF-1 α , and VEGF expression [254]
Sulforaphane	Inhibited angiogenesis through activation of FOXO transcription factors and inhibition of MEK/ERK and PI3K/AKT pathways in HUVECs [256]
Taxol	Inhibited VEGF production in human leukemic cell lines [257].
γ -Tocotrienol	Inhibited cobalt(II) chloride-induced accumulation of HIF-1 α and the paracrine secretion of VEGF in human gastric adenocarcinoma SGC-7901 cell line through downregulation of ERK-1/2 pathway [258]
Ursolic acid	Inhibited capillary formation, reduced serum level of VEGF, NO, and proinflammatory cytokines in C57BL/6 mice bearing B16-F10 melanoma cells [259]
Vanillin	Suppressed HGF-induced tumor cell angiogenesis in a mouse model through inhibition of PI3K/AKT signaling and VEGF expression [260]

AITC allyl isothiocyanate, AKT AKT8 virus oncogene cellular homolog, Ang2 angiopoietin 2, AP-1 activator protein 1, CAM chorioallantoic membrane, COX cyclooxygenase, CRC colorectal carcinoma, c-Src cellular Rous sarcoma oncogene cellular homolog, EAT Ehrlich ascites tumor, EC endothelial cell, EGCG epigallocatechin-3-gallate, ERK extracellular signal-regulated kinase, FAK focal adhesion kinase, FGF2 fibroblast growth factor 2, FOXO forkhead homeobox type O, HGF hepatocyte growth factor, HIF-1 hypoxia-inducible factor 1, HUVEC human umbilical vein endothelial cell, IL-8 interleukin 8, MAPK mitogen-activated protein kinase, MEK MAPK/ERK kinase, NF- κ B nuclear factor kappa B, NO nitric oxide, NOS nitric oxide synthase, PI3K phosphoinositide 3 kinase, STAT signal transducer and activator of transcription, VEGF vascular endothelial growth factor, VEGFR2 VEGF receptor 2

antiangiogenic activity by inhibiting VEGF production and HIF- α expression [257]. In a human gastric adenocarcinoma SGC-7901 cell line, γ -tocotrienol inhibited cobalt(II) chloride-induced accumulation of HIF-1 α and paracrine secretion of VEGF. A decrease in VEGF secretion was associated with decreased activation of ERK-1/ERK-2 [258]. The antiangiogenic activity of ursolic acid was shown recently; ursolic acid inhibited capillary formation

in C57BL/6 mice bearing B16-F10 melanoma cells. Levels of serum VEGF, NO, and proinflammatory cytokines were significantly reduced in ursolic-acid-treated animals compared with those in control animals [259]. Vanillin, a food flavoring agent, suppressed hepatocyte-growth-factor-induced tumor cell angiogenesis in a mouse model that was mediated through inhibition of PI3K/AKT signaling and VEGF expression [260].

4 Summary, conclusions, and future perspective

Tumorigenesis is a multistep process regulated by multiple signaling pathways and is the target of numerous anticancer therapies. Many of the cellular pathways overlap, showing a high degree of redundancy within the system. Therefore, targeting a single molecule might ultimately have little or no effect, resulting in the need for either combination therapy or multitargeted therapy. Nutraceuticals are inexpensive, safe, and readily available and have multitargeted potential and have thus drawn considerable attention during the past decade. As this review has shown, the future of nutraceuticals as a cancer-fighting weapon seems promising. Some nutraceuticals have already progressed from the bench to the bedside either alone or in combination with existing therapy. However, greater attention is needed to clarify the following important issues.

First, several agents can inhibit as well as potentiate tumorigenesis. Numerous articles and commentaries have been published on this topic [261–266]. The fact that a given molecular component may act in opposite ways further complicates the interpretation of data. For example, although NF- κ B has a negative effect on apoptosis in most situations, it may induce apoptosis under special circumstances, depending on the stimulus, cell type, and NF- κ B subunit involved [261, 267, 268]. *Second*, although most studies have suggested that nutraceuticals kill cancer cells selectively, several studies have reported that nutraceuticals kill normal cells as well. *Third*, the efficacy of most nutraceuticals has been tested only in preclinical conditions, either *in vitro* or *in vivo*. Whether beneficial effects will be seen in humans is largely unknown. To date, success has been limited to a few cancers and to a few molecules. *Fourth*, resistance to chemoprevention is emerging, and thus a better understanding of the pathways involved in mediating tumor progression in various circumstances is necessary. *Fifth*, in some cases, disruption of a particular pathway can lead to pathological changes. For example, the antiangiogenic feature in resveratrol is not only limited to pathological angiogenesis but also affects physiological angiogenesis [251]. *Sixth*, in various cases, it is possible that the observations obtained in experimental settings were not due to the nutraceutical itself but were instead due to the intermediate formed during the process. *Finally*, low potency and poor bioavailability of nutraceuticals pose further challenges to scientists. Introducing synthetic analogs of nutraceuticals could be a solution for these potency and bioavailability limitations. For example, the potency of synthetic curcumin analog EF24 was shown to be approximately 10-fold greater than that of natural curcumin [269].

In light of the above facts, it is clear that we need a much better understanding of the efficacy of nutraceuticals in cancer prevention. Future studies should focus on careful

and accurate characterization of nutraceuticals, better elucidation of the molecular mechanisms involved in their actions, determination of their efficacy by *in vivo* studies using proper animal models of cancer, and demonstration of their safety and effectiveness in clinical trials.

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